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(57) Abstract

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I), the variables are as defined and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.

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Heteroaryl Derivatives

Background of the Invention

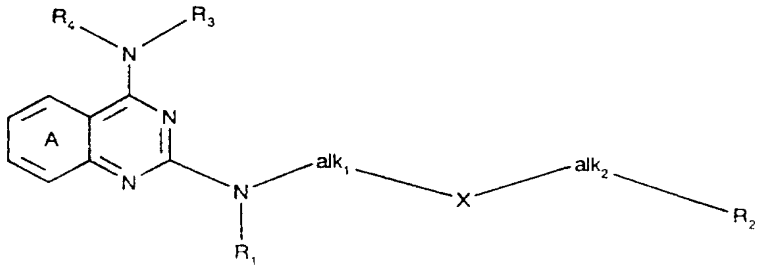
Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family of peptides and is one of the most abundant and widely distributed peptides at the central and peripheral nervous system. NPY acts as a neurotransmitter playing an important role in the regulation of various diseases. Intensive evaluations lead to the finding that multiple NPY receptors are existing being responsible for different physiological and pharmacological activities. Recently, a new NPY receptor subtype has been characterized and cloned, designated as Y5 receptor. It has been demonstrated that the pharmacological function associated with Y5 relates, for example, to obesity and eating disorders. Accordingly, the provision of compounds which act as antagonists of this receptor subtype represents a promisable approach in the regulation of diseases or disorders, such as obesity and eating/food intake disorders.

Summary of the Invention

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions and to new compounds having Y5 antagonistic properties.

Detailed Description of the Invention

The present invention relates to a method of prophylaxis and treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I)



in which

alk_1 and alk_2, independently of one another, represent, independently of one another, a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$C(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a pharmaceutically accetable salt thereof; and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.

The compounds I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C_1-C_4-alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C_1-C_4-alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid.

Corresponding acid addition salts can also be formed having, if desired, an additionally present basic centre. The compounds (I) having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts, are also included.

(Carbocyclic or heterocyclic) aryl in (carbocyclic or heterocyclic) aryl or aryloxy, respectively, represents, for example, phenyl, biphenylyl, naphthyl or an appropriate 5- or 6-membered and monocyclic radical or an appropriate bicyclic heteroaryl radical which, in each case, have up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate bicyclic heterocyclic aryls are, for example, indolyl, indazolyl, benzofuryl, benzothienyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl. Appropriate aromatic radicals, including ring A, are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group as given above. Preferred substituents of corresponding aryl radicals (including of ring A) are, for example, halogen, lower alkyl, halo-lower alkyl, lower alkoxy, oxy-lower alkylene-oxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

(Carbocyclic or heterocyclic) aroyl is in particular benzoyl, naphthoyl, furoyl, thenoyl, or pyridoyl.

(Carbocyclic or heterocyclic) aryl-lower alkanoyl in (carbocyclic or heterocyclic) aryl-lower alkanoyloxy or (carbocyclic or heterocyclic) aryl -lower alkanoyl is in particular phenyl-lower alkanoyl, naphthyl-lower alkanoyl, or pyridyl-lower alkanoyl,

(Carbocyclic or heterocyclic) aryl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-lower alkyl.

(Carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl is in particular phenyl-, naphthyl- or pyridyl-lower alkoxy.

Lower alkyl which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl, amino-lower alkyl, or corresponding N- or N,N- substituted amino-lower alkyl.

An amino group which is mono-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl is in particular lower alkylamino, C_3-C_8-cycloalkyl-amino, C_3-C_8-cycloalkyl-loweralkyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkylamino.

An amino group which is, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl is in particular di-lower alkylamino, di-C_3-C_8-cycloalkyl-amino, di-(C_3-C_8-cycloalkyl-lower alkyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino, lower alkyl-C_3-C_8-cycloalkyl-amino, lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino.

Lower alkyl which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl,

carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0, the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_3H, -SO_2-R and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkoxy-lower alkoxy-carbonyl-lower alkyl, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, or corresponding N- or N,N-substituted carbamoyl-lower alkyl.

Lower alkoxy which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy, amino-lower alkoxy, or corresponding N- or N,N- substituted amino-lower alkoxy.

Lower alkoxy which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0, the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_3H, -SO_2-R and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, lower alkoxy-lower alkoxy-carbonyl-lower alkoxy, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, or corresponding N- or N,N-substituted carbamoyl-lower alkoxy.

Substituted lower alkyl or lower alkoxy, respectively, is mono- or poly-substituted, e.g. di- or tri-substituted.

The group of formula -N(R_3)(R_4) in which R_3 and R_4 together represent lower alkylene which is condensedat two adjacent carbon atoms with a benzene ring represents, for example, lower alkylene-phenylene-lower alkylene-amino, such as 3,4-dihydro-1*H*-isoquinolin-2-yl.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds, in each case, in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkyl is in particular C_1-C_7- alkyl, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals. C_1-C_4-alkyl is preferred.

Lower alkenyl is in particular C_3-C_7-alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl. C_3-C_5-alkenyl is preferred.

Lower alkynyl is in particular C_3-C_7-alkynyl and is preferably propargyl.

Lower alkoxy is in particular C_1-C_7-alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. C_1-C_4-alkoxy is preferred.

Lower alkenyloxy is in particular C_3-C_7-alkenyloxy, preferably allyloxycarbonyl, while lower alkynyloxy is in particular C_3-C_5-alkynyloxy, such as propargyloxy.

Oxy-lower alkylene-oxy is in particular oxy-C_1-$_4$-alkylene-oxy, preferably oxy-methylene-oxy or oxy-ethylene-oxy.

Lower alkanoyloxy is in particular C_2-C_7-alkanoyloxy, such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy. C_2-C_5-alkanoyloxy is preferred.

Lower alkanoyl is in particular C_2-C_7-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C_2-C_5-alkanoyl is preferred.

Naphthoyl is 1- or 2-naphthoyl, furoyl 2- or 3-furoyl, thenoyl 2- or 3-thenyl, and pyridoyl 2-, 3-, or 4-pyridoyl.

C_3-C_8-Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

C_3-C_8-Cycloalkyl-lower alkyl is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkyl, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkyl. Preferred is cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

C_3-C_8-Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C_3-C_8-Cycloalkyl-lower alkoxy is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkoxy. Preferred is cyclopropylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy.

Lower alkylene is in particular C_1-C_7-alkylene, in particular C_1-C_5-alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and butylene and also 1,2-propylene, 2-methyl-1,3-propylene, 3-methyl-1,5-pentylene and 2,2-dimethyl-1,3-propylene. C_3-C_5-alkylene is preferred. In case of alk_1 or alk_2, respectively, lower alkylene preferably is -$(CH_2)_p$- the integer p being 1-3. Lower alkylene in an substituted amino group preferably is 1,2-ethylene, 1,3-

propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 2-methyl-1,3-propylene, or 2-methyl-butylene, or 3-methyl-1,5-pentylene.

Amino which di-substituted by lower alkylene is in particular C_3-C_7-alkyleneamino, preferably 1-azidino, 1-pyrrolidino or 1-piperidino.

Amino which di-substituted by lower alkylene which is interrupted by O, $S(O)_n$ or NR_0 is in particular morpholino, thiomorpholino or the mono- or di-oxide thereof, or 4-R_0-piperazino.

Lower alkanesulfonyl is in particular C_1-C_4-alkoxy-C_1-C_5-alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropyloxyethoxycarbonyl.

Lower alkoxycarbonyl is in particular C_2-C_8-alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C_2-C_5-alkoxycarbonyl is preferred.

Lower alkoxy-lower alkoxy-carbonyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl and is, for example, methoxy- or ethoxy-ethoxy-alkoxycarbonyl.

Hydroxy-lower alkyl is in particular hydroxy-C_1-C_4-alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. Furthermore, hydroxy-lower alkyl may exhibit two hydroxy groups, such as 3-hydroxy-1-hydroxymethyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C_1-C_4-alkoxy, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy-lower alkoxy is in particular C_1-C_4-alkoxy-C_1-C_4-alkoxy and is, for example, 2-methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Amino which di-substituted by lower alkylene and is condensed at two adjacent carbon atom with a benzene ring is in particular C_2-C_6-cycloalkylenemino which is is condensed at

two adjacent carbon atom with a benzene ring. Preferred is indolin-1-yl or 1,2,3,4-tetrahydro-quinolin-1-yl.

Halo-lower alkyl is in particular halo-C_1-C_4-alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkoxy is in particular halo-C_1-C_4-alkoxy, such as trifluoromethoxy, 1,1,2-trifluoro-2-chloroethoxy or chloromethoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C_1-C_4-alkyl, such as phenoxy-methyl, 2-phenoxy-ethyl, 1- or 2-naphthyloxy-methyl, or 2-, 3-, or 4-pyridyloxy-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkyl, such as phenyl-methyl, 2-phenyl-ethyl, 1- or 2-naphthyl-methyl, or 2-, 3-, or 4-pyridyl-methyl.

Naphthyl is in particular 1- or 2-naphthyl; furyl 2- or 3-furyl; thienyl 2- or 3-thienyl; pyridyl 2-, 3- or 4-pyridyl, indolyl, indazolyl e.g. 6-1(H)-indazolyl, benzofuryl e.g.2-, 3- or 5-benzofuranyl, benzothienyl e.g. 2-, 3-, or 5-benzothienyl, benzimidazolyl e.g. 1-, 2- or 5-benzimidazolyl, quinolinyl e.g. 2-, 4- 5-, 6-,7-, or 8-quinolinyl, isoquinolinyl e.g. 1-, 3-, 4-, or 6-isoquinolyl, or quinazolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl.

Amino-lower alkyl is in particular amino-C_1-C_7-alkyl, preferably amino-C_1-C_4-alkyl, such as aminomethyl, 2-aminoethyl or 3-aminopropyl.

Lower alkylamino is in particular C_1-C_7-alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C_1-C_4-alkylamino is preferred.

C_3-C_8-Cycloalkyl-amino is in particular C_3-C_6-cycloalkyl-amino and is, for example, cyclopropyl-, cyclopentyl and cyclohexyl-amino.

C_3-C_8-Cycloalkyl-lower alkylamino is in particular C_3-C_8-cycloalkyl-C_1-C_7-alkylamino and is, for example, cyclopropylmethyl-amino or cyclohexylmethyl-

amino. C_3-C_8-Cycloalkyl-C_1-C_4-alkylamino is preferred.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino is in particular phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl)-amino, preferably benzyl-amino, 2-phenethyl-amino, 1- or 2-naphthylmethyl-amino, or 2-, 3-, or 4-pyridylmethyl-amino.

Di-lower alkylamino is in particular di-C_1-C_4-alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

Di-C_3-C_8-cycloalkyl-amino is in particular di-C_3-C_6-cycloalkylamino, preferably cyclopropylamino, cyclopentylamino or cyclohexylamino.

Di-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular di-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)-amino, preferably cyclopropylmethyl-amino, cyclopentylmethyl-amino or cyclohexylmethyl-amino.

Di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4- alkyl)-amino, preferably di-benzyl-amino, di-(2-phenethyl)-amino, di-(1- or 2-naphthylmethyl)-amino, or di-(2-, 3-, or 4-pyridylmethyl)-amino.

Lower alkyl-C_3-C_8-cycloalkyl-amino is in particular C_1-C_4-alkyl-C_3-C_6-cycloalkyl-amino, preferably nethyl-cyclopropyl-amino, methyl-cyclopentyl-amino or methyl-cyclohexyl-amino.

Lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)amino, preferably nethyl-cyclopropylmethyl-amino, methyl-cyclopentylmethyl-amino or methyl-cyclohexylmethyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino, such as (m)ethyl-phenyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl)-amino, such as (m)ethyl-benzyl-amino or (m)ethyl-(2-phenethyl)-amino.

Carboxy-lower alkyl is in particular carboxy-C_1-C_4-alkyl, such as carboxy-methyl, 2-carboxy-ethyl, or 3-carboxy-propyl.

Lower alkoxy-carbonyl-lower alkyl is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as (m)ethoxycarbonyl-methyl, 2-(m)ethoxycarbonyl-ethyl or 2-pivaloyl-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as 2-methoxy-ethoxycarbonyl-methyl or 2-(2-ethoxy-ethoxycarbonyl)-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as benzyloxycarbonyl-methyl or 2-(2-phenethyloxy-carbonyl)-ethyl.

Carbamoyl-lower alkyl is in particular carbamoyl-C_1-C_4-alkyl, such as carbamoyl-methyl, 2-carbamoyl-ethyl or 3-carbamoyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C_1-C_4alkoxy, such as hydroxymethoxy, 2-hydroxyethoxy or 3-hydroxypropoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkoxy is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C_1-C_4-alkoxy, such as phenoxy-methoxy, 2-phenoxy-ethoxy, 1- or 2-naphthyloxy-methoxy, or 2-, 3-, or 4-pyridyloxy-methoxy.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkoxy, such as phenyl-methoxy, 2-phenyl-ethoxy, 1- or 2-naphthyl-methoxy, or 2-, 3-, or 4-pyridyl-methoxy.

Amino-lower alkoxy is in particular amino-C_1-C_4-alkoxy, such as aminomethoxy, 2-aminoethoxy, or 3-amino-propoxy.

Carboxy-lower alkoxy is in particular carboxy-C_1-C_4-alkoxy, such as carboxy-methoxy, 2-carboxy-ethoxy, or 3-carboxy-propyloxy.

Lower alkoxy-carbonyl-lower alkoxy is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxycarbonyl-methoxy, 2-methoxycarbonyl-ethyl, or 2-(2-ethoxycarbonyl)-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkoxy is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxymethoxycarbonyl-methoxy, 2-ethoxy-methoxycarbonyl-ethyl, or 2-[(2-ethoxy-ethoxycarbonyl)]-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as benzyloxycarbonyl-methoxy, phenethyloxycarbonyl-methoxy, 2-(benzyloxycarbonyl)-ethoxy, or 2-(2-phenethyloxycarbonyl)-ethoxy.

Carbamoyl-lower alkoxy is in particular carbamoyl-C_1-C_4-alkoxy, such as carbamoyl-methoxy, 2-carbamoyl-ethoxy, or 3-carbamoyl-propyloxy.

Obesity, for example, is a wide-spread phenomena which e.g. causes a variety of pathological symptoms or influences the overall state of health. Also associated therewith are considerable socio-economic investments and a heavy financial burden for managed health care organisations. The problem to be solved is to present an approach to systemically treat obesity or related diseases or disorders. Surprisingly, it has been manifested that the modulation of the NPY receptor subtype Y5 leads to a control of the eating behavior.

Extensive pharmacological investigations have shown that the compounds (I) and their pharmaceutically acceptable salts, for example, are useful as antagonists of the neuropeptide Y5 receptor subtype.

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family with wide-spread distribution throughout the mammalian nervous system. NPY and its relatives (peptide YY or PYY, and pancreatic polypeptide or PP) elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". The role of NPY as the most powerful stimulant of feeding behavior yet described is thought to occur primarily through activation of the hypothalamic "atypical Y1"

receptor. This receptor is unique in that its classification is based solely on feeding behavior data, rather than radioligand binding data, unlike the Y1, Y2, Y3, and Y4 (or PP) receptors, each of which are described previously in both radioligand binding and functional assays. ^{125}I-PYY-based expression cloning technique may be used to isolate a rat hypothalamic cDNA encoding an "atypical Y1" receptor referred to herein as the Y5 subtype. Y5 homolog may be isolated and characterized of from human hippocampus. Protein sequence analysis reveals that the Y5 receptor belongs to the G protein- coupled receptor superfamily. Both the human and rat homolog display $\leq$ 42% identity in transmembrane domains with the previously cloned "Y-type" receptors. Rat brain localization studies using in situ hybridization techniques verify the existence of Y5 receptor mRNA in rat hypothalamus. Pharmacological evaluation reveals the following similarities between the Y5 and the "atypical Y1" receptor. 1) Peptides bind to the Y5 receptor with a rank order of potency identical to that described for the feeding response: NPY ^{3} NPY_{2-36} = PYY = [Leu^{31}, Pro^{34}]NPY >> NPY_{13-36}. 2) The Y5 receptor is negatively coupled to cAMP accumulation, as has been proposed for the "atypical Y1" receptor. 3) Peptides activate the Y5 receptor with a rank order of potency identical to that described for the feeding response. 4) The reported feeding "modulator" [D-Trp^{32}]NPY binds selectively to the Y5 receptor and subsequently activated the receptor. 5) Both the Y5 and the "atypical Y1" receptors are sensitive to deletions or modifications in the midregion of NPY and related peptide ligands.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system. NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark, J.T., Kalra, P.S., Crowley, W.R., and Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 115: 427-429, 1984; Levine, A.S., and Morley, J.E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. Peptides 5: 1025-1029; Stanley, B.G., and Leibowitz, S.F.; (1984) Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci. 35: 2635-2642). Direct injection into the hypothalamus of satiated rats, for example, can increase food intake up to 10-fold over a 4-hour period (Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993;

Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308). Any credible means of studying or controlling NPY-dependent feeding behavior, however, must necessarily be highly specific as NPY can act through at least 5 pharmacologically defined receptor subtypes to elicit a wide variety of physiological functions (Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167). It is therefore vital that knowledge of the molecular biology and structural diversity of the individual receptor subtypes be understood as part of a rational drug design approach to develop subtype selective compounds. A brief review of NPY receptor pharmacology is summarized below and also in Table 1.

TABLE 1: Pharmacologically defined receptors for NPY and related pancreatic polypeptides.

Rank orders of affinity for key peptides (NPY, PYY, PP, [Leu^{31},Pro^{34}]NPY, NPY_{2-36}, and NPY_{13-36}) are based on previously reported binding and functional data (Schwartz, T.W., J. Fuhlendorff, L.L.Kjems, M.S. Kristensen, M. Vervelde, M. O'Hare, J.L. Krstenansky, and B. Bjornholm. (1990). Signal epitopes in the three-dimensional structure of neuropeptide Y. Ann. N.Y. Acad. Sci. 611: 35-47; Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082; Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167; Wahlestedt, C., and D.J. Reis. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352). Missing peptides in the series reflect a lack of published information.

TABLE 1

Receptor	Affinity (pK_i or pEC_{50})					
	11 to 10	10 to 9	9 to 8	8 to 7	7 to 6	< 6
Y1	NPY PYY [Leu^{31},Pro^{34}] NPY		NPY_{2-36}	NPY_{13-36}	PP	
Y2		PYY NPY NPY_{2-36}	NPY_{13-36}			[Leu^{31},Pro^{34}] NPY PP
Y3		NPY	[Pro^{34}] NPY	NPY_{13-36}PP		PYY
Y4	PP	PYY [Leu^{31},Pro^{34}] NPY	NPY NPY_{2-36}	NPY_{13-36}		
Y5		PYY NPY NPY_{2-36} [Leu^{31},Pro^{34}] NPY		NPY_{13-36}		

NPY Receptor Pharmacology

NPY receptor pharmacology has historically been based on structure/activity relationships within the pancreatic polypeptide family. The entire family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, M.C. (1991). Receptors for neuropeptide Y: multiple subtypes and multiple second messengers. Trends Pharmacol.: 12: 389-394; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr^{36} (or Y^{36} in the single letter code). The striking conservation of Y^{36} has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt, C., L. Edvinsson, E. Ekblad, and R. Hakanson. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y_1 and Y_2 receptors. In: Neuronal messengers in vascular function, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987)), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

The Y1 receptor recognizes NPY = PYY >> PP (Grundemar et al., 1992). The receptor requires both the N- and the C-terminal regions of the peptides for optimal recognition. Exchange of Gln^{34} in NPY or PYY with the analogous residue from PP (Pro^{34}), however, is well-tolerated. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar, D., A.G. Blomqvist, F. Yee, E. Jazin, H. Yoo, and C. Wahlestedt. (1992). Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. J. Biol. Chem. 267: 10935-10938; Herzog, H., Y.J. Hort, H.J. Ball, G. Hayes, J. Shine, and L. Selbie. (1992). Cloned human neuropeptide Y receptor couples to two different second messenger systems. Proc. Natl. Acad. Sci. USA 89, 5794-5798; Eva, C., Oberto, A., Sprengel, R. and E. Genazzani. (1992). The murine NPY-1 receptor gene: structure and delineation of tissue specific expression. FEBS lett. 314: 285-288; Eva, C., Keinanen, K., Monyer, H., Seeburg, P., and Sprengel, R. (1990). Molecular cloning of a novel G protein-coupled receptor that may belong to the neuropeptide receptor family. FEBS Lett. 271, 80-84). The Y2 receptor recognizes PYY ~ NPY >> PP and is relatively tolerant of N-terminal deletion (Grundemar, L. and RI Hakanson (1994). Neuropeptide Y effector systems:

perspectives for drug development. Trends. Pharmacol. 15:153-159). The receptor has a strict requirement for structure in the C-terminus (Arg^{33}-Gln^{34}-Arg^{35}-Tyr^{36}-NH_2); exchange of Gln^{34} with Pro^{34}, as in PP, is not well tolerated. The Y2 receptor has recently been cloned. The Y3 receptor is characterized by a strong preference for NPY over PYY and PP (Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082). [Pro^{34}]NPY is reasonably well tolerated even though PP, which also contains Pro^{34}, does not bind well to the Y3 receptor. This receptor (Y3) has not yet been cloned. The Y4 receptor binds PP > PYY > NPY. Like the Y1, the Y4 requires both the N- and the C-terminal regions of the peptides for optimal recognition. The "atypical Y1" or "feeding" receptor is defined exclusively by injection of several pancreatic polypeptide analogs into the paraventricular nucleus of the rat hypothalamus which stimulates feeding behavior with the following rank order: $NPY_{2-36} \geq$ NPY ~ PYY ~ [Leu^{31},Pro^{34}]NPY > NPY_{13-36} (Kalra, S.P., Dube, M.G., Fournier, A., and Kalra, P.S. (1991). Structure-function analysis of stimulation of food intake by neuropeptide Y: Effects of receptor agonists. Physiology & Behavior 50: 5-9; Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The profile is similar to that of a Y1-like receptor except for the anomalous ability of NPY_{2-36} to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report by Balasubramaniam, A., Sheriff, S., Johnson, M.E., Prabhakaran, M., Huang, Y., Fischer, J.E., and Chance, W.T. (1994). [D-Trp^{32}]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 311-815 showed that feeding can be regulated by [D-Trp^{32}]NPY. While this peptide is presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp^{32}]NPY on feeding. [D-Trp^{32}]NPY thereby represents another diagnostic tool for receptor identification.

This plasmid (pcEXV-hY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. 75943.

The plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the rat Y5 receptor as to permit expression thereof has been designated as pcEXV-rY5 (ATCC Accession No. 75944).

This plasmid (pcEXV-rY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. CRL 75944.

A method for determining whether a ligand can specifically bind to a Y5 receptor comprises contacting a cell transfected with and expressing DNA encoding the Y5 receptor with the ligand under conditions permitting binding of ligands to such receptor, detecting the presence of any such ligand specifically bound to the Y5 receptor, and thereby determining whether the ligand specifically binds to the Y5 receptor.

A method for determining whether a ligand is a Y5 receptor antagonist comprises contacting a cell transfected with and expressing DNA encoding a Y5 receptor with the ligand in the presence of a known Y5 receptor agonist, such as PYY or NPY, under conditions permitting the activation of a functional Y5 receptor response, detecting a decrease in Y5 receptor activity, and thereby determining whether the ligand is a Y5 receptor antagonist.

In an embodiment of the above-described methods, the cell is non-neuronal in origin. In a further embodiment, the non-neuronal cell is a COS-7 cell, 293 human embryonic kidney cell, NIH-3T3 cell or L-M(TK-) cell.

The cell lines are transfected with a vector which is adapted for expression in a mammalian cell which comprises the regulatory elements necessary for expression of the DNA in the mammalian cell operatively linked to the DNA encoding the mammalian Y5 receptor as to permit expression thereof.

For example, such plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the human

Y5 receptor as to permit expression thereof designated pcEXV-hY5 (ATCC Accession No. 75943).

Experimental Details

MATERIALS AND METHODS

cDNA Cloning

Total RNA was prepared by a modification of the guanidine thiocyanate method (Kingston, 1987), from 5 grams of rat hypothalamus (Rockland, Gilbertsville, PA). Poly A^+RNA was purified with a FastTrack kit (Invitrogen Corp., San Diego, CA). Double stranded (ds) cDNA was synthesized from 7 mg of poly A^+ RNA according to Gubler and Hoffman (Gubler, U abd B.J. Hoffman. (1983). A simple and very efficient method for generating cDNA libraries. Gene. 25, 263-269), except that ligase was omitted in the second strand cDNA synthesis. The resulting DS cDNA was ligated to BstxI/EcoRI adaptors (Invitrogen Corp.), the excess of adaptors was removed by chromatography on Sephacryl 500 HR (Pharmacia®-LKB) and the ds-cDNA size selected on a Gen-Pak Fax HPLC column (Millipore Corp., Milford, MA). High molecular weight fractions were ligated in pEXJ.BS (A cDNA cloning expression vector derived from pcEXV-3; Okayama, H. and P. Berg (1983). A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. Mol. Cell. Biol. 3: 280-289; Miller, J. and Germain, R.N. (1986). Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. J. Exp. Med. 164: 1478-1489) cut by BstxI as described by Aruffo and Seed (Aruffo, A. and Seed, B. (1987). Molecular cloning of a CD28 cDNA by a high efficiency COS cell expression system. PNAS, 84, 8573-8577). The ligated DNA was electroporated in E.Coli MC 1061 F^+ (Gene Pulser, Biorad). A total of 3.4×10^6 independent clones with an insert mean size of 2.7 kb could be generated. The library was plated on Petri dishes (Ampicillin selection) in pools of 6.9 to 8.2×10^3 independent clones. After 18 hours amplification, the bacteria from each pool were scraped, resuspended in 4 ml of LB media and 1.5 ml processed for plasmid purification with a QIAprep-8 plasmid kit (Qiagen Inc, Chatsworth, CA). 1 ml aliquots of each bacterial pool were stored at -85°C in 20% glycerol.

Isolation of a cDNA clone encoding an atypical rat hypothalamic NPY5 receptor

DNA from pools of » 7500 independent clones was transfected into COS-7 cells by a modification of the DEAE-dextran procedure (Warden, D. and H.V. Thorne. (1968). Infectivity of polyoma virus DNA for mouse embryo cells in presence of diethylaminoethyl-dextran. J. Gen. Virol. 3, 371). COS-7 cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 2 mM L-glutamine (DMEM-C) at 37°C in 5% CO_2. The cells were seeded one day before transfection at a density of 30,000 cells/cm^2 on Lab-Tek chamber slides (1 chamber, Permanox slide from Nunc Inc., Naperville, IL). On the next day, cells were washed twice with PBS, 735 ml of transfection cocktail was added containing 1/10 of the DNA from each pool and DEAE-dextran (500 mg/ml) in Opti-MEM I serum free media (Gibco®BRL LifeTechnologies Inc. Grand Island, NY). After a 30 min. incubation at 37°C, 3 ml of chloroquine (80 mM in DMEM-C) was added and the cells incubated a further 2.5 hours at 37°C. The media was aspirated from each chamber and 2 ml of 10% DMSO in DMEM-C added. After 2.5 min. incubation at room temperature, the media was aspirated, each chamber washed once with 2 ml PBS, the cells incubated 48 hours in DMEM-C and the binding assay was performed on the slides. After one wash with PBS, positive pools were identified by incubating the cells with 1 nM ($3x10^6$ cpm per slide) of porcine [^{125}I]-PYY (NEN; SA=2200 Ci/mmole) in 20 mM Hepes-NaOH pH 7.4, CaCl2 1.26 mM, MgSO4 0.81 mM, KH_2PO_4 0.44 mM, KCL 5.4, NaCl 10 mM, .1% BSA, 0.1% bacitracin for 1 hour at room temperature. After six washes (three seconds each) in binding buffer without ligand, the monolayers were fixed in 2.5% glutaraldehyde in PBS for five minutes, washed twice for two minutes in PBS, dehydrated in ethanol baths for two minutes each (70, 80, 95, 100%) and air dried. The slides were then dipped in 100% photoemulsion (Kodak® type NTB2) at 42°C and exposed in the dark for 48 hours at 4°c in light proof boxes containing drierite. Slides were developed for three minutes in Kodak® D19 developer (32 g/l of water), rinsed in water, fixed in Kodak® fixer for 5 minutes, rinsed in water, air dried and mounted with Aqua-Mount (Lerner Laboratories, Pittsburgh, PA). Slides were screened at 25x total magnification. A single clone, CG-18, was isolated by SIB selection as described (Mc Cormick, 1987). DS-DNA was sequenced with a Sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer. Nucleotide and peptide sequence analysis were performed with GCG programs (Genetics Computer group, Madison, WI).

Isolation of the human Y5 homolog

Using rat oligonucleotide primers in TM 3 (sense primer; position 484-509 in SEQ ID NO:1) and in TM 6 (antisense primer; position 1219-1243 in SEQ ID NO: 1), a human hippocampal cDNA library has been screened using the polymerase chain reaction. 1 μl (4×10^6 bacteria) of each of 450 amplified pools containing each »5000 independent clones and representing a total of 2.2×10^6 was subjected directly to 40 cycles of PCR and the resulting products analyzed by agarose gel electrophoresis. One of three positive pools was analyzed further and by sib selection a single cDNA clone was isolated and characterized. This cDNA turned out to be full length and in the correct orientation for expression. DS-DNA was sequenced with a sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer.

Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LMT(k)- cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:10 every 3-4 days.

Stable Transfection

Human Y5 and rat Y5 receptors were co-transfected with a G-418 resistant gene into mouse fibroblast LMT(k)- cells by a calcium phosphate transfection method (Cullen, B.

(1987). Use of eurkaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704). Stably transfected cells were selected with G-418.

EXPERIMENTAL RESULTS

cDNA Cloning

In order to clone a rat hypothalamic "atypical" NPY receptor subtype, applicants used an expression cloning strategy in COS-7 cells (Gearing et al, 1989; Kluxen, F.W., Bruns, C. and Lubbert H. (1992). Expression cloning of a rat brain somatostatin receptor cDNA. Proc. Natl. Acad. Sci. USA 89, 4618-4622; Kieffer, B., Befort, K., Gaveriaux-Ruff, C. and Hirth, C.G. (1992). The
δ-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc. natl. Acad. Sci. USA 89, 12048-12052). This strategy was chosen for its extreme sensitivity since it allows detection of a single "receptor positive" cell by direct microscopic autoradiography. Since the "atypical" receptor has only been described in feeding behavior studies involving injection of NPY and NPY related ligands in rat hypothalamus (see introduction), applicants first examined its binding profile by running competitive displacement studies of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ on membranes prepared from rat hypothalamus. The competitive displacement data indicate: 1) Human PP is able to displace 20% of the bound ^{125}I-PYY with an IC_{50} of 11 nM (Fig. 1 and Table 2). As can be seen in table 5, this value does not fit with the isolated rat Y1, Y2 and Y4 clones and could therefore correspond to another NPY/PYY receptor subtype. 2) [Leu$_{31}$, Pro$_{34}$] NPY (a Y1 specific ligand) is able to displace with high affinity (IC_{50} of 0.38) 27% of the bound ^{125}I-PYY$_{3-36}$ ligand (a Y2 specific ligand) (Fig. 2 and table 2). These data provide the first evidence based on a binding assay that rat hypothalamic membranes could carry an NPY receptor subtype with a mixed Y1/Y2 pharmacology (referred to as the "atypical" subtype) which fits with the pharmacology defined in feeding behavior studies.

TABLE 2: Pharmacological profile of the rat hypothalamus.

Binding data reflect competitive displacement of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ from rat hypothalamic membranes. Peptides were tested at concentrations ranging from 0.001 nM to 100 nM unless noted. The IC_{50} value corresponding to 50% displacement, and the

percentage of displacement relative to that produced by 300 nM human NPY, were determined by nonlinear regression analysis. Data shown are representative of at least two independent experiments.

TABLE 2

Peptide	IC_{50} Values, nM (% NPY-produced displacement)	
	^{125}I-PYY	^{125}I-PYY_{3-36}
human NPY	0.82 (100%)	1.5 (100%)
human NPY_{2-36}	2.3 (100%)	1.2 (100%)
human [Leu^{31},Pro^{34}]NPY	0.21 (44%) 340 (56%)	0.38 (27%) 250 (73%)
human PYY	1.3 (100%)	0.29 (100%)
human PP	11 (20%)	untested

Based on the above data, a rat hypothalamic cDNA library of 3 x 10^6 independent recombinants with a 2.7 kb average insert size was fractionated into 450 pools of »7500 independent clones. All pools were tested in a binding assay with ^{125}I-PYY as described (Y2 patent). Seven pools gave rise to positive cells in the screening assay (# 81, 92, 147, 246, 254, 290, 312). Since Y1, Y2, Y4 and Y5 receptor subtypes (by PCR or binding analysis) are expressed in rat hypothalamus, applicants analyzed the DNA of positive pools by PCR with rat Y1, Y2 and Y4 specific primers. Pools # 147, 246, 254 and 312 turned out to contain cDNAs encoding a Y1 receptor, pool # 290 turned out to encode a Y2 subtype, but pools # 81 and 92 were negative by PCR analysis for Y1, Y2 and Y4 and therefore likely contained a cDNA encoding a new rat hypothalamic NPY receptor (Y5). Pools # 81 and 92 later turned out to contain an identical NPY receptor cDNA. Pool 92 was subjected to sib selection as described until a single clone was isolated (designated CG-18).

The isolated clone carries a 2.8 kb cDNA. This cDNA contains an open reading frame between nucleotides 779 and 2146 that encodes a 456 amino acid protein. The long 5'

untranslated region could be involved in the regulation of translation efficiency or mRNA stability. The flanking sequence around the putative initiation codon does not conform to the Kozak consensus sequence for optimal translation initiation (Kozak, M. (1989). The scanning model for translation: an update. J. Cell Biol. 108, 229-241; Kozak, M. (1991). Structural features in eukaryotic mRNAs that modulate the initiation of translation. J. Biol. Chem. 266, 19867-19870). The hydrophobicity plot displayed seven hydrophobic, putative membrane spanning regions which makes the rat hypothalamic Y5 receptor a member of the G-protein coupled superfamily. The nucleotide and deduced amino acid sequences are shown in SEQ ID NOS: 1 and 2, respectively.

Localization studies show that the Y5 mRNA is present in several areas of the rat hippocampus. Assuming a comparable localization in human brain, applicants screened a human hippocampal cDNA library with rat oligonucleotide primers which were shown to yield a DNA band of the expected size in a PCR reaction run on human hippocampal cDNA. Using this PCR screening strategy (Gerald et al, 1994, submitted for publication), three positive pools were identified. One of these pools was analyzed further, and an isolated clone was purified by sib selection. The isolated clone (CG-19) turned out to contain a full length cDNA cloned in the correct orientation for functional expression (see below). The human Y5 nucleotide and deduced amino acid sequences are shown in SEQ ID NOS 3 and 4, respectively. When compared to the rat Y5 receptor the human sequence shows 84.1% nucleotide identity and 87.2% amino acid identity. The rat protein sequence is one amino acid longer at the very end of both amino and carboxy tails of the receptor when compared to the rat. Both pharmacological profiles and functional characteristics of the rat and human Y5 receptor subtype homologs may be expected to match closely.

When the human and rat Y5 receptor sequences were compared to other NPY receptor subtypes or to other human G protein-coupled receptor subtypes, both overall and transmembrane domain identities are very low, showing that the Y5 receptor genes are not closely related to any other previously characterized cDNAs.

The compounds according to the present invention and their pharmaceutically acceptable salts have proven to exhibit pronounced and selective affinity to the Y5 receptor subtype (shown in Y5 binding test) and in vitro and in vivo antagonistic properties. These properties are shown in vitro by their ability to inhibit NPY-induced calcium increase in stable

transfected cells expressing the Y5 receptor and in vivo by their ability to inhibit food intake induced by intracerebroventricular application of NPY or 24 h food deprivation in conscious rats.

Binding experiments

The selective affinity of the compounds according to the present invention to the Y5 receptor is detected in a Y5 binding assay using LM(tk-)-h-NPY5-7 cells which stably express the human NPY Y5 receptor or HEK-293 cells stably expressing the rat NPY Y5 receptor.

The following buffers are used for the preparation of membranes and for binding assay:

a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediamine tetraacetate (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH: 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM); buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM), KH_2PO_4 (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

Cells are washed in phosphate buffered saline and harvested using a rubber policeman. The cells are homogenised using a Polytron homogeniser (3 bursts of 8 seconds) in ice-cold hypotonic buffer (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged at 32,000 x g for 20 min at 4°C. The pellets are resuspended in the same buffer and recentrifuged. The final pellets are suspended in buffer 2. Protein concentration is measured by the method of Bradford using the Pierce reagent [PIERCE, Rockford, USA], with bovine serum albumin as standard. The crude membrane preparation is aliquoted, flash-frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

^{125}I-[Pro^{34}]hPYY (60 pM, Anawa, Wangen, Switzerland) dissolved in buffer 3 is used as radioligand. All test compounds are dissolved in dimethyl sulfoxide (DMSO) at 10^{-2} M and diluted to 10^{-3} M in buffer 3. Subsequent dilutions are in buffer 3 plus 10% DMSO. Incubations are performed in Millipore Multiscreen FC filter plates [Millipore, Bedford, USA]. The filters in each well are pretreated with 2% polyethyleneimine for 30 min and rinsed once with 300 microL buffer 3 before use. The following are pipetted into each well: 20 microL buffer 3, 25 microL ^{125}I-[Pro^{34}]hPYY [SAXON, Hannover, Germany] (600 pM); 25 microL

test compound (or binding buffer for the controls); 180 microL crude membrane suspension (approximately 5 microg protein). Incubations are performed at room temperature for 2h. Non-specific binding is defined as the binding remaining in the presence of 1 microM [Pro^{34}]hPYY. The incubations are terminated by rapid filtration and washing four times with 300microL phosphate buffered saline. The filters are removed from the wells, placed into plastic tubes and assayed for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC50 values of the compounds according to this invention at the human Y5 receptor range especially between about 0.1 nM and about 10 microM.

Measurements of calcium transient

For the determination of in vitro antagonistic properties of the compounds according to the present invention, stably transfected LM(tk-)-hY5-7 cells are used in which a NPY-induced calcium transient is measured as described below. Cells are harvested in a medium containing EDTA (0.5 mM) and phosphate buffered saline (PBS). Cells are then washed in phosphate buffered saline solution and loaded for 90 min at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxy methylester, supplemented with pluronic acid as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, $MgCl_2$ 1 mM, KCl 5.4 mM, NaH_4PO_4 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM HEPES 10 mM, insulin 10 U/l, BSA 0.1% at for 90 min at room temperature. After centrifugation the cells are resuspended in the cell culture buffer at a concentration of 3-4 million cells/ml and supplemented with 200 microM sulfinpyrazone.

Calcium transients are measured at room temperature in a millititer plate using a Cytofluor 2350 (Millipore) with wavelength settings at 485 nm for excitation and 530 nm for emission. 180 microL of cells suspension are preincubated in the presence of various amounts of compounds dissolved in 2 microL DMSO in triplicates (or 2 microL DMSO for the controls) for 5 min and then NPY is added at a final concentration of 100 nM. The compound concentrations giving 50% inhibition of the maximum of the Ca transients are then calculated.

In this cell system, NPY induces Ca transients with an EC50 of 50 nM. The data are analyzed using a Microsoft Excel software. The concentrations which cause a 50% inhibition

of the initial control values are given as IC50 values. The IC50 values are determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The property of the compounds according to the present invention and their pharmaceutically acceptable salts to inhibit NPY-induced increase intracellular calcium indicates their antagonistic properties with IC50 values ranging especially between about 0.1 nM and about 10 microM. Representatives are, for example, the final products of working examples 3, 4 and 11, for which following IC50 values [μM/L] were determined: 0.02 (Ex. 3); 0.1 (Ex. 4); 0.32 (Ex. 11).

Measurements of NPY-induced food intake in conscious rats

In addition this antagonistic property of the Y5 receptor subtype is also observed in-vivo in conscious rats by their ability to inhibit NPY-induced food intake. For these determinations food intake is measured in normal satiated rats after intracerebroventricular application (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] in the presence or absence of the compounds according to the present invention. Male Sprague-Dawley rats weighing 180-220 g are used for all experiments. They are individually housed in stainless steel cages and maintained on a 11:13 h light-dark schedule (lights off at 1800 h) under controlled temperature (21-23 °C) at all times. Water and food (NAFAG lab chow pellets) [NAFAG, Gossau, Switzerland] are available ad libitum.

Under pentobarbital [VETERINARIA AB, Zürich, Switzerland] anesthesia, all rats are implanted with a stainless steel guide cannula targeted at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0 mm below interaural line, are : -0.8 mm anterior and +1.3 mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extended the guide cannulas -3.8 mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments.

Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (icv) injection of angiotensin II . Only rats which drink at least 2.5 ml of water within 30 min after angiotensin II injection are used in the feeding studies. Injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland] in a volume of 5 μl. The ACSF contains NaCl 124 mM, KCl 3.75 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 2.0 mM, KH_4PO_4 0.22 mM, $NaHCO_3$ 26 mM and glucose 10 mM. NPY (300 pmole) is administered by the

intracerebroventricular route 10-60 minutes after administration of compounds or vehicle DMSO/water (10%,v/v) or cremophor/water (20%,v/v) [SIGMA, Buchs, Switzerland].

Food intake is measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each time point indicated in the figures and replaced with a new set of preweighed pellets.
All results are presented as means ±SEM. Statistical analysis is performed by analysis of variance using Student-Newman-Keuls test.

The compounds according to the present invention inhibit NPY-induced food intake in rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

Measurements of food intake in 24 hours food deprived rats

Based on the observation that food deprivation induces an increase in the hypothalamic NPY levels, it is assumed that NPY mediates food intake induced by food deprivation. Thus, the compounds according to the present invention are also tested in rats after 24 hours food deprivation. These experiments are conducted with male Sprague-Dawley (CIBA-GEIGY AG, Sisseln, Switzerland] rats weighing between 220 and 250 g. The animals are housed in individual cages for the duration of the study and allowed free access to normal food together with tap water. The animals are maintained in room with a 12 h light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the individual cages the rats undergo a 2-4 days equilibration period, during which they are habituated to their new environment and to eating a powdered or pellet diet [NAFAG, Gossau, Switzerland]. At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8.00 a.m. At the end of the fasting period the animals are injected intraperitoneally, intravenously or orally either with the compounds according to the present invention or an equivalent volume of vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) and 10-60 min later the food is returned to them. Food intake at various time periods is monitored over the following 24 hour period. Inhibition of food intake by the compounds according to the present invention is given in percentage of the respective control vehicle-treated rats.
The compounds according to the present invention inhibit food intake in this food deprived rat model in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration. Representatives are, for example, the final

products of working examples 1 and 2, for which an inhibition of food intake of 57% or 46%, respectively, versus the respective control vehicle-treated animals after i.p. application of 30 mg/kg was determined.

Measurements of food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention can also be shown in Zucker obese rats, an art-known animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to powdered food together with tap water. The animals are maintained in a room with a 12 hour light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with the compounds according to the present invention or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v).

The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

The above experiments clearly demonstrate that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that corresponding antagonists can be used for the treatment of obesity and related disorders [*Nature, Vol. 382, 168-171 (1996)*].

The compounds according to the present invention can inhibit food intake induced either by intracerebroventricular application of NPY or by food deprivation or as well as spontaneous eating in the Zucker obese rat. Thus, the compounds according to the present invention can especially be used for the prophylaxis and treatment of disorders or diseases associated with the Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain and additionally in the treatment of sexual/reproductive

disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The compounds according to the present invention act as antagonists of neuropeptide Y (NPY) binding at the Y5 receptor subtype. By virtue of their Y5 receptor antagonistic property, the compounds of the formula (I) and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in pharmaceutical compositions which are employed, for example, for the prophylaxis and treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and

additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates especially to a method of prophylaxis and treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) lower alkoxy or lower alkoxy-lower alkoxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and N-substituted carbamoyl;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0];

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) substituted amino;
(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy or lower alkoxy-lower alkoxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

R_3 represents

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and N-substituted carbamoyl;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, or -CO-;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower

alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) substituted amino;
(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl, pyrrolyl, imidazolyl, or pyridyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, phenyl, phenyl-lower alkyl, or lower alkyl which is substituted by di-lower alkylamino;
(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;
(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl;
(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy or di-lower alkyl-amino;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, or -CO-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, phenyl, or phenyl-lower alkyl;
(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl;
(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents hydrogen, lower alkyl, lower alkyl which substituted by lower alkoxy or di-lower alkylamino, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, or -CO-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent C_2-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, phenyl, phenyl-lower alkyl, or pyrrolyl, imidazolyl;
(ii) amino, amino which is mono-substituted by C_3-C_6-cycloalkyl, amino which is disubstituted by lower alkyl or by C_4-C_6-alkylene or amino which is mono-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1; or
(iii) a group selected from -NR_1-SO_2-R , -SO_2-R, or -SO_2-NR_1-R, [R_1 being hydrogen; R being C_1-C_4-alkyl, or naphthyl, and the group -NR_1(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

and, in each case,

R_3 represents hydrogen, lower alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-lower alkyl, phenyl-lower alkyl, or lower alkyl which is substituted by lower alkoxy or by di-lower alkylamino; and

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene or -O-;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent C_2-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents a group -NH-SO_2-R or -NH-SO_2-N(R)(R_1)[R being C_1-C_4-alkyl, or naphthyl, or the group -N(R)(R_1) represents amino which is mono-substituted by C_1-C_4-alkyl, by phenyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by NR_0, R_0 being C_1-C_4-alkyl}];

and, in each case,

R_3 represents hydrogen, lower alkyl or lower alkyl which is substituted by loewr alkoxy or di-lower alkylamino; and

R_4 represents hydrogen;

X represents a single bond or 1,2-ethenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-lower alkyl, phenyl, phenyl-lower alkyl, or pyrrolyl, imidazolyl;

(ii) amino, amino which is mono-substituted by C_3-C_6-cycloalkyl, amino which is disubstituted by lower alkyl or by C_4-C_6-alkylene or amino which is mono-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

(iii) a group selected from -NR_1-SO_2-R, R being lower phenyl or naphthyl;

R_3 represents hydrogen, C_3-C_6-cycloalkyl-lower alkyl, phenyl-lower alkyl, lower alkyl which substituted by di-lower alkylamino, C_3-C_6-cycloalkyl, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond or -O-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents -SO_2-R or -SO_2-NH-R and R being C_1-C_4-alkyl, especially methyl, or naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond or ethenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents (i) phenyl which is substituted by halogen, especially 4-halo-phenyl, or pyrrolyl, especially 1-pyrrolyl or (ii) -NH-SO_2-R and R being naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents ethylene;

alk_2 represent C_2-C_3-alkylene;

R_2 represents -SO_2-NH-R and R being naphthyl, especially 1- or 2-naphthyl;

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents phenyl which is substituted by halogen, especially 4-chloro-phenyl, or pyrrolyl, especially 1-pyrrolyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention likewise relates to a new compound of formula (I) or a salt thereof as described hereinbefore or hereinafter.

The present invention relates to a new compound of formula (I) or a salt thereof, e.g. in which

alk_1 and alk_2, independently of one another, represent, independently of one another, a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0

or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2-$;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and $-S(O)_n-R$;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl,

lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl represents (phenyl-, naphthyl- or pyridyl)-lower alkoxy-carbonyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkyl represents phenyl-, naphthyl- or pyridyl-lower alkyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-oxy represents phenoxy, naphthyloxy, or pyridyloxy;

wherein, in each case, (carbocyclic or heterocyclic) aryl-loweralkanoyl represents (phenyl-, naphthyl- or pyridyl)-lower alkanoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(ii) substituted amino;

(iii) lower alkoxy or lower alkoxy-lower alkoxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from $-NR_1-CO-R$, $-NR_1-SO_2-R$, $-NR_1-SO_2-NR_1-R$, $-SO_2-R$, $-SO_2-NR_1-R$, or $-SO_2-NR_1-CO-R$, [R being as defined below and R_1 being as defined above, or the group $-N(R)(R_1)$ represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_1(X_2)(X_3)$ wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula $-X_4-(CO)_p-(CH_2)_o-$, $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$, or $-(CH_2)_s-X_4-CO-(CH_2)_t-$; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula $-CO-(CH_2)_u-$; [X_4 being $-CH_2-$, $-N(R_1)-$ or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2-$;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and N-substituted carbamoyl;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0];

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) substituted amino;
(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(ii) substituted amino;

(iii) hydroxy, lower alkoxy or lower alkoxy-lower alkoxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, $-NR_1$-CO-R, $-NR_1$-SO_2-R, $-NR_1$-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

R_3 represents

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and N-substituted carbamoyl;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, or -CO-;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic)

aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) substituted amino;

(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl represents (phenyl-, naphthyl- or pyridyl)-lower alkoxy-carbonyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkyl represents phenyl-, naphthyl- or pyridyl-lower alkyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-oxy represents phenoxy, naphthyloxy, or pyridyloxy;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkanoyl represents (phenyl-, naphthyl- or pyridyl)-lower alkanoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl, pyrrolyl, imidazolyl, or pyridyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl;

(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy or di-lower alkyl-amino;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, or- -CO-;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl;

(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents hydrogen, lower alkyl, C_3-C_3-cycloalkyl, C_3-C_3-cycloalkyl-lower alkyl, phenyl-lower alkyl, lower alkyl which substituted by lower alkoxy or di-lower alkylamino, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, or -CO-;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-lower alkyl, phenyl-lower alkyl, phenyl, pyrrolyl, or imidazolyl;

(ii) amino, amino which is mono-substituted by C_3-C_6-cycloalkyl, amino which is disubstituted by lower alkyl or by C_4-C_6-alkylene or amino which is mono-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

(iii) a group selected from -NR_1-SO_2-R, R being lower phenyl or naphthyl;

R_3 represents hydrogen, C_3-C_6-cycloalkyl-lower alkyl, phenyl-lower alkyl, lower alkyl which substituted by di-lower alkylamino, C_3-C_6-cycloalkyl, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond or -O-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent C_2-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, or C_1-C_4-alkoxy, especially methoxy; or a group selected from -NH-SO_2-R , -SO_2-R, or -SO_2-NH-R, [R being C_1-C_4-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

and, in each case,

R_3 represents hydrogen, lower alkyl, or lower alkyl which is substituted by lower alkoxy or by di-lower alkylamino; and

R_4 represents hydrogen;

X represents a single bond or 1,2-ethenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents (i) phenyl which is substituted by halogen,especially 4-halo-phenyl, or pyrrolyl, especially 1-pyrrolyl or (ii) -NH-SO_2-R and R being naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent C_2-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents a group -NH-SO_2-R or -NH-SO_2-N(R)(R_1)[R being C_1-C_4-alkyl, or naphthyl, or the group -N(R)(R_1) represents amino which is mono-substituted by C_1-C_4-alkyl, by phenyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by NR_0, R_0 being C_1-C_4-alkyl}];

and, in each case,

R_3 represents hydrogen, lower alkyl or lower alkyl which is substituted by loewr alkoxy or di-lower alkylamino; and

R_4 represents hydrogen;

X represents a single bond or 1,2-ethenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a new a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents -SO_2-R or -SO_2-NH-R and R being C_1-C_4-alkyl, especially methyl, or naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond or ethenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents (i) phenyl which is substituted by halogen, especially 4-halo-phenyl, or pyrrolyl, especially 1-pyrrolyl or (ii) -NH-SO_2-R and R being naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents phenyl which is substituted by halogen, especially 4-chloro-phenyl, or pyrrolyl, especially 1-pyrrolyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents ethylene;

alk_2 represent C_2-C_3-alkylene;

R_2 represents -SO_2-NH-R and R being naphthyl, especially 1- or 2-naphthyl;

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

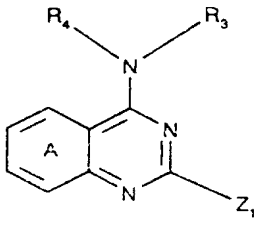
X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates in particular to the novel compounds shown in the examples and to the modes of preparation described therein.

The invention relates to processes for the preparation of the compounds according to the invention. The preparation of new compounds of the formula (I) and their salts comprises, for example,

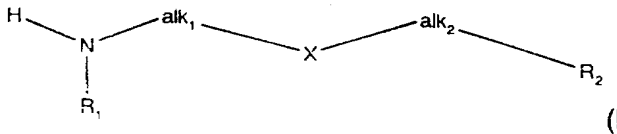
(a) reacting a compound of formula (IIa) or a salt thereof



(IIa)

in which Z_1 represents a leaving group,

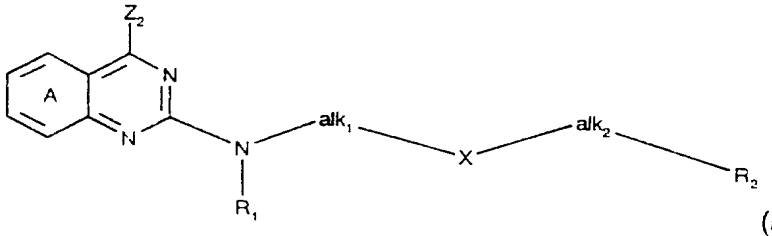
with a compound of formula (IIb) or a salt thereof



(IIb)

or

(b) reacting a compound of formula (IIIa) or a salt thereof



(IIIa)

in which Z_2 is a leaving group

with a compound of formula $HN(R_3)(R_4)$ (IIIb) or a salt thereof,

and, if desired, converting a compound I obtainable according to the process or in another manner, in free form or in salt form, into another compound I, separating a mixture of isomers obtainable according to the process and isolating the desired isomer and/or converting a free compound I obtainable according to the

process into a salt or converting a salt of a compound I obtainable according to the process into the free compound I or into another salt.

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. The person skilled in the pertinent art is especially referred to the methods as outlined in the working examples based upon which the person skilled in the art is enabled to carry out the manufacture of the compounds of formula (I).

Salts of starting materials which have at least one basic centre, for example of the formula IIIb, are appropriate acid addition salts, while salts of starting materials which have an acidic group, for example of the formula (IIb), are present as salts with bases, in each case as mentioned above in connection with corresponding salts of the formula I.

A leaving group Z_1 or Z_2, respectively, is, for example, reactive esterified hydroxy, or is R'-S(O)$_u$- [the integer u being 0, 1 or 2 and R' being lower alkyl, halo-lower alkyl or aryl, such as methyl, trifluoromethyl or p-toluyl], or is lower alkoxy. Reactive esterified hydroxyl Z_4 is in particular hydroxyl esterified with a strong inorganic acid or organic sulfonic acid, for example halogen, such as chlorine, bromine or iodine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, C_1-C_7-alkane-sulfonyloxy which is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethanesulfonyloxy, C_5-C_7cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy which is unsubstituted or substituted, for example by C_1-C_7alkyl or halogen, for example p-bromobenzene- or p-toluenesulfonyloxy. Preferred Z_1 or Z_2 is chloro, bromo or iodo, methanesulfonyloxy or trifluoromethanesulfonyloxy, or p-toluenesulfonyloxy, or

methylthio or methoxy.

The reactions of process variants (a) and (b) are carried out, if necessary, in the presence of a base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, lithium triphenylmethylide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, N-methylpiperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU).

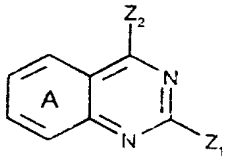
The starting material of fomulae (IIa), (IIb), (IIIa), and (IIIb) is essentially known or is accessible analogously to preparation processes known per se.

Starting material of the formula (IIa) is, for example, described, for example, in US Patent No. 5,064,833.

The starting material of formula (IIb) in which R_2 represents N-acylated or N-alkylated amino, such as a group of formula $-NR_1-CO-O-R$, $-NR_1-CO-R$, $-NR_1-CO-NR_1-R$, $-NR_1-SO_2-R$,$-NR_1-SO_2-NR_1-R$, or N-substituted amino, is accessible, for example, by N-acylating or by N-alkylating, respectively, a, preferably N-protected, compound of the formula $NH(R_1)-alk_1-X-alk_2-Z_3$ (IIc) in which Z_3 represents a group which is convertable to R_2, such as amino, carboxy, or hydroxy. Conventional protecting groups may be used, for example, t-butoxycarbonyl which will be splitt off after the N-acylation or the N-alkylation, respectively. The starting material of formula (IIb) in which R_2 represents carbamoyl or N-substituted carbamoyl, or esterified carboxy, can be manufactured starting from a compound of formula (IIc) in which Z_3 represents carboxy. The esterification or amidation can be carried out in a manner known per

se. Starting fom a compound of formula (IIc) in which Z_3 is hydroxy, corresponding etherified or esterified derivatices are accessible using etherification or esterifaction methods known in the art.

The starting material of formula (IIIa) is accessible, for example, by selectively converting the 4-Z_2-group into a group which is desactivated, for example, by selectively hydrolyzing a compound of formula (IIIc)



(IIa)

or a salt thereof to form a corresponding 4-hydroxy-compound which is in the next step reacted with a compound of formula (IIb) to introduce the corresponding side chain into position 2 of the quinazolin ring. Reactivation of the 4-position, for example, by reaction with a halogenating agent, such as $POCl_3$, leads to corresponding compounds of formula (IIIa).

The invention likewise relates to pharmaceutical preparations which contain the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention or pharmaceutically acceptable salts thereof are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated

tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the abovementioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or

suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 250 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg .

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner. Temperatures are indicated in degrees Celsius.

Solvent systems (v/v/v):

A 1: 1:1 hexanes/ethylacetate

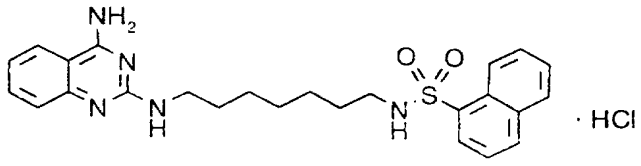
A2: 2:1 hexanes/ethylacetate

A3:	90:10:	1dichloromethane / methanol / ammonium hydroxide
A4:	80:20: 4	dichloromethane / methanol / ammonium hydroxide
A5:	180:20:2:1	dichloromethane / methanol / water / acetic acid
B1:	9:1	dichloromethane/methanol
B2:	10:1	toluene / ethyl acetate
C1:	90:10:1	dichloromethane/methanol/ammonium hydroxide
C2:	80:20:2	dichloromethane/methanol/ammonium hydroxide
C3:	2:1	hexanes / ethyl acetate
C4:	1:1	hexanes / ethyl acetate
D1:	6:3:1	ethyl acetate / ethanol / ammonium hydroxide
E1:	9:1	ethyl acetate / methanol

Abbreviations:

HCl	hydrochloric acid
ml	milliliter
NaOH	sodium hydroxide
RaNi	Raney Nickel
Pd/C	Palladiunm on charcoal
min	minute(s)
h	hour(s)
m.p.	melting point
ESI-MS:	electro-spray ionization mass spectroscopy
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
Rf	retention factor on a thin layer chromatography plate

Example 1: Naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide hydrochloride



A solution of 0.298 g of naphthalene-1-sulfonic acid (7-amino-heptyl)-amide and 0.167 g of 2-chloro-quinazolin-4-ylamine (see: US 3,956,495) in 16 ml of isopentylalcohol is heated up

to 120 °C for 15 hours. Concentration of the reaction mixture followed by chromatography on silica gel (B1) gives 0.192 g of product, which is taken up in dichloromethane and treated at 0 °C with 3 ml of a 4 N HCl solution in dioxane. After concentration *in vacuo*, naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide is obtained as its hydrochloride salt, melting at 100-110 °C. Rf(B1) 0.27; FAB-MS: $(M+H)^+ = 464$.

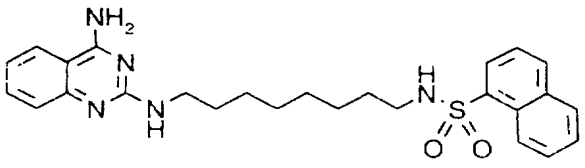
a) [7-(Naphthalene-1-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester

A solution of naphthalene-1-sulfonylchloride (3.00 g) and diisopropylethylamine (4.53 ml) in 80 ml of acetonitrile is cooled to 0 °C and treated with (7-amino-heptyl)-carbamic acid *tert*-butyl ester (3.04 g) in acetonitrile (20 ml). The reaction mixture is stirred at ambient temperature until completion of the reaction. The solution is concentrated and the residue is partitioned between dichloromethane and water. The organics are dried over magnesium sulfate and concentrated to an oil. Chromatography on silica gel (A2) provides [7-(naphthalene-1-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester as a white powder and melting at 79-81 °C. Rf(A2) 0.32.

b) Naphthalene-1-sulfonic acid (7-amino-heptyl)-amide

A solution of [7-(naphthalene-1-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester (4.70 g) in dichloromethane (30 ml) is treated at 0 °C by slow addition of a 4 N HCl solution in dioxane (30 ml). Under completion, the reaction mixture is concentrated *in vacuo*, the residue is taken up in a 1 N sodium hydroxide solution and is extracted with dichloromethane. The organics are dried over magnesium sulfate and concentrated to yield naphthalene-1-sulfonic acid (7-amino-heptyl)-amide as a white powder and melting at 67-68 °C. Rf(C1) 0.26.

Example 2: Naphthalene-1-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide



A solution of naphthalene-1-sulfonic acid (8-amino-octyl)-amide (0.334 g) and 2-chloro--quinazolin-4-ylamine (0.180 g) in 20 ml of isopentylalcohol is heated up to 120 °C for 15

hours. Concentration of the reaction mixture followed by chromatography on silica gel (B1) gives naphthalene-1-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide as a yellow powder and melting at 80-85 °C. Rf(B1) 0.24; FAB-MS: $(M+H)^+$ = 478.

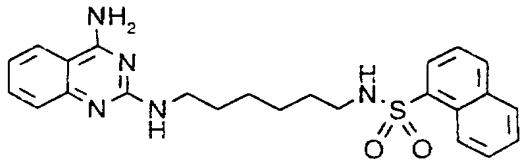
a) [8-(Naphthalene-1-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester

Following the procedure described in Example 1a, (8-amino-octyl)-carbamic acid *tert*-butyl ester (3.00 g) and naphthalene-1-sulfonylchloride (4.17 g) are converted to [8-(naphthalene-1-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester as an oil. Rf(A2) 0.27.

b) Naphthalene-1-sulfonic acid (8-amino-octyl)-amide

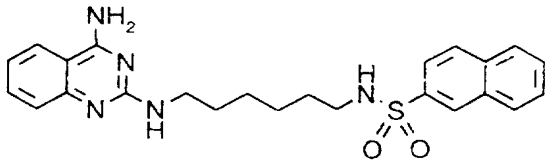
[8-(Naphthalene-1-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester (4.55 g) is converted according to Example 1b to naphthalene-1-sulfonic acid (8-amino-octyl)-amide as a brown oil. Rf(C2) 0.29.

Example 3: Naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide



Following the procedure described in Example 2, naphthalene-1-sulfonic acid (6-amino--hexyl)-amide (0.450 g) and 2-chloro-quinazolin-4-ylamine (0.264 g) yield naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide as a white powder, melting at 98-101 °C. Rf(B1) 0.28; FAB-MS: $(M+H)^+$ = 450.

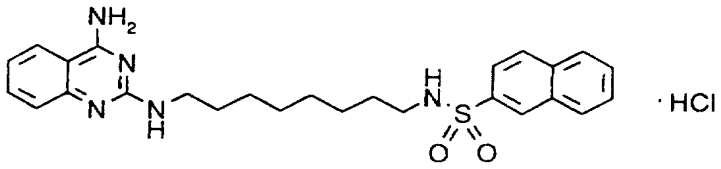
Example 4: Naphthalene-2-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide



Following the procedure described in Example 2, naphthalene-2-sulfonic acid (6-amino-hexyl)-amide (0.350 g) and 2-chloro-quinazolin-4-ylamine (0.205 g) yield naphthalene-2-

sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide as a white powder, melting at 93-96 °C. Rf(B1) 0.18; FAB-MS: $(M+H)^+$ = 450.

Example 5: Naphthalene-2-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide hydrochoride



Following the procedure described in Example 1, naphthalene-2-sulfonic acid (8-amino-octyl)-amide (0.350 g) and 2-chloro-quinazolin-4-ylamine (0.188 g) yield naphthalene-2-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide hydrochoride melting at 80-86 °C. Rf(B1) 0.22; FAB-MS: $(M+H)^+$ = 478.

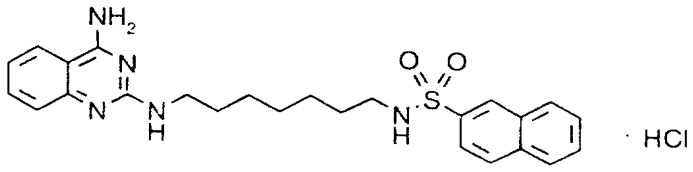
a) [8-(Naphthalene-2-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester

Following the procedure described in Example 1a, (8-amino-octyl)-carbamic acid *tert*-butyl ester (3.00 g) and naphthalene-2-sulfonylchloride (4.17 g) are converted to [8-(naphthalene-2-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester melting at 91-92 °C. Rf(A2) 0.20.

b) Naphthalene-2-sulfonic acid (8-amino-octyl)-amide

[8-(Naphthalene-2-sulfonylamino)-octyl]-carbamic acid *tert*-butyl ester (5.00 g) is converted according to Example 1b to naphthalene-2-sulfonic acid (8-amino-octyl)-amide as a tan powder melting at 70-71 °C . Rf(C1) 0.07.

Example 6: Naphthalene-2-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide hydrochloride



Following the procedure described in Example 1, naphthalene-2-sulfonic acid (8-amino-octyl)-amide (0.300 g) and 2-chloro-quinazolin-4-ylamine (0.168 g) yield naphthalene-2-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide hydrochloride melting at 88-96 °C. Rf(B1) 0.22; FAB-MS: $(M+H)^+$ = 464.

a) [7-(Naphthalene-2-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester

Following the procedure described in Example 1a, (7-amino-heptyl)-carbamic acid *tert*-butyl ester (2.03 g) and 2-naphthalene sulfonylchloride (2.00 g) are converted to [7-(naphthalene-2-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester melting at 62-63 °C. Rf(A1) 0.42.

b) Naphthalene-2-sulfonic acid (7-amino-heptyl)-amide

[7-(Naphthalene-2-sulfonylamino)-heptyl]-carbamic acid *tert*-butyl ester (2.07 g) is converted according to Example 1b to naphthalene-2-sulfonic acid (7-amino-heptyl)-amide melting at 81-84 °C . Rf(C1) 0.07.

Example 7: In a manner analogous to that described hereinbefore it is also possible to manufacture following compounds:

Naphthalene-1-sulfonic acid [5-(4-amino-quinazolin-2-ylamino)-3,3-dimethyl-pentyl]-amide;

naphthalene-1-sulfonic acid {3-{1-[3-(4-amino-quinazolin-2-ylamino)-propyl]-cyclopentyl}-propyl}-amide;

naphthalene-1-sulfonic acid {5-[1-(4-amino-quinazolin-2-ylamino)-cyclopentyl}-pentyl}-amide;

naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-6-methyl-heptyl]-amide;

trans-naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-enyl]-amide;

cis-naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-enyl]-amide;

naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-ynyl]-amide;

naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-5-methoxy-hexyl]-amide;

naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-7-methoxy-heptyl]-amide;

naphthalene-1-sulfonic acid [5-(4-amino-quinazolin-2-ylamino)-3,3-dimethyl-pentyl]-amide;

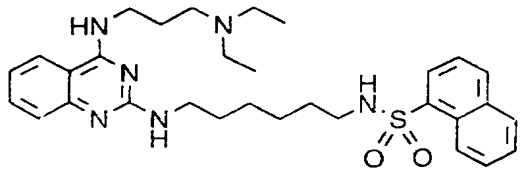
naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-6-methyl-heptyl]-amide;

naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-ynyl]-amide;

cis-Naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-enyl]-amide;

trans-naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hex-3-enyl]-amide;
naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-4,4-dimethyl-heptyl]-amide;
trans-naphthalene-1-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-oct-4-enyl]-amide;
benzenesulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide;
N-[6-(4-amino-quinazolin-2-yl-amino)-hexyl]-(N,N-dimethylamino)-sulfonamide;
N-[6-(4-amino-quinazolin-2-yl-amino)-hexyl]-(piperidin1-yl)-sulfonamide;
N-[6-(4-amino-quinazolin-2-yl-amino)-hexyl]-(4-methyl-piperazin-1-yl)-sulfonamide;
N-[6-(4-amino-quinazolin-2-yl-amino)-hexyl]-(N-methylamino)-sulfonamide;
naphthalene-1-sulfonic acid [6-(4-amino-8-methoxy-quinazolin-2-ylamino)-hexyl]-amide;
naphthalene-2-sulfonic acid [6-(4-amino-8-methoxy-quinazolin-2-ylamino)-hexyl]-amide;
N-[6-(4-amino-8-methoxy-quinazolin-2-yl-amino)-hexyl]-(N,N-dimethylamino)-sulfonamide;
N-[6-(4-amino-8-methoxy-quinazolin-2-yl-amino)-hexyl]-(piperidin1-yl)-sulfonamide;
naphthalene-1-sulfonic acid {6-[4-(2-methoxy-ethylamino)-quinazolin-2-yl-amino]-hexyl}-amide;
naphthalene-1-sulfonic acid {6-[4-(2-dimethylamino-ethylamino)-quinazolin-2-yl-amino]-hexyl}-amide;
naphthalene-1-sulfonic acid [6-(4-methylamino-quinazolin-2-yl-amino)-hexyl]-amide;
naphthalene-1-sulfonic acid [6-(4-dimethylamino-quinazolin-2-yl-amino)-hexyl]-amide;
naphthalene-1-sulfonic acid [6-(4-methylamino-8-methoxy-quinazolin-2-yl-amino)-hexyl]-amide;
naphthalene-1-sulfonic acid {6-[4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-yl-amino]-hexyl}-amide;
naphthalene-2-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-methyl-amide;
naphthalene-1-sulfonic acid {6-[(4-methylamino-quinazolin-2-yl)-methyl-amino]-hexyl}-amide;
naphthalene-1-sulfonic acid {6-[(4-amino-8-methoxy-quinazolin-2-yl)-methyl-amino]-hexyl}-amide.

Example 8: Naphthalene-1-sulfonic acid {6-[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-amide hydrochloride



A solution of N(2)-(6-amino-hexyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.47 g) and diisopropylethylamine (0.22 ml) in acetonitrile (8 ml) at 0 °C is treated with 1-naphthalene-sulfonylchloride (0.115 g) in acetonitrile (2 ml). Upon completion, the reaction mixture is concentrated, the residue is partitioned between dichloromethane and brine. The organic phase is dried over sodium sulfate, concentrated and chromatographed (silica gel, C1). Treatment of the resulting material in dichloromethane (10 ml) at 0 °C with 4N HCl in dioxane (2 ml) followed by evaporation of the solvent gives naphthalene-1-sulfonic acid {6-[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-amide hydrochloride as a foam. Rf(C1) 0.43; ESI-MS: $(M+H)^+$= 563.

The starting material can be prepared, for example, as follows:

a) N-(2-Chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

A suspension of 2,4-dichloro-quinazoline (30 g) in isopropanol (200 ml) is treated by dropwise addition of a solution of N,N-diethyl-1,3-diaminopropane (26.1 ml) in isopropanol (50 ml) in an exothermic reaction. The reaction mixture is concentrated *in vacuo* and the residue is stirred overnight in isopropylether/isopropanol. The resulting suspension is collected by filtration and dried *in vacuo* to give N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride as a powder melting at 163-164 °C. Rf(C1) 0.32.

b) {6-[4-(3-Diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-carbamic acid *tert*-butyl ester

A mixture of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride (2.24 g), N-*tert.*-butoxy-carbonyl-1,6-diamino-hexane (1.47 g), diisopropylethylamine (3.5 ml) and phenol (9.6 g) is heated to 150 °C for 3 h to produce a melt. The reaction mixture is taken up in dichloromethane, washed with a 1N aqueous NaOH solution, brine and dried over sodium sulfate. Concentration *in vacuo* followed by chromatography (silica gel, C1)

gives {6-[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-carbamic acid *tert.*-butyl ester as an oil. Rf(C2) 0.69; ESI-MS: $(M+H)^+$= 473.

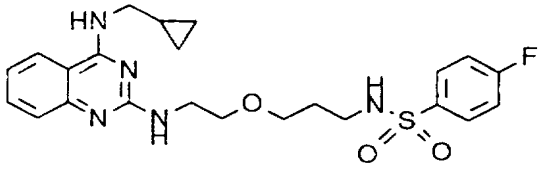
c) N(2)-(6-Amino-hexyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine

A solution of {6-[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-carbamic acid *tert.*-butyl ester (0.2 g) in dichloromethane (10 ml) is cooled to 0 °C and treated by slow addition of trifluoroacetic acid (10 ml). Upon completion of the reaction, the solution is concentrated *in vacuo* and the residue is chromatographed (silica gel, C2) to give N(2)-(6-amino-hexyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine as an oil. Rf(C2) 0.29; ESI-MS: $(M+H)^+$= 373.

Example 9: Naphthalene-1-sulfonic acid [6-(4-amino-6-bromo-quinazolin-2-ylamino)-hexyl]-amide hydrochloride

Following the procedure described in Example 2; 6-bromo-2-chloro-quinazolin-4-yl-amine (prepared as described in *Khim.-Farm. Zh.* **1987**, *21*, 802) (0.259 g) and naphthalene-1-sulfonic acid (6-amino-hexyl)-amide (0.355 g) yields naphthalene-1-sulfonic acid [6-(4-amino-6-bromo-quinazolin-2-ylamino)-hexyl]-amide hydrochloride as an amorphous solid: Rf(A5) 0.42; FAB-MS: $(M+H)^+$ = 528.

Example 10: N-(3-{2-[4-(Cyclopropylmethyl-amino)-quinazolin-2-ylamino]-ethoxy}-propyl)-4-fluoro-benzenesulfonylamide



A solution of 4-cyclopropylmethylamino-2-chloroquinazoline (0.862 g), N-[3-(2-amino--ethoxy)-propyl]-4-fluoro-benzenesulfonamide trifluoroacetic acid salt (1.44 g) and diisopropylethylamine (1.89 ml) in isopentanol (20 ml) is stirred at 120 °C for 19 h. The solvent is removed under reduced pressure and the residue is added to 1N aqueous NaOH and extracted with dichloromethane. The combined extracts are dried over sodium sulfate, concentrated *in vacuo* and chromatographed to give N-(3-{2-[4-(cyclopropylmethyl-amino)-

quinazolin-2-ylamino]-ethoxy}-propyl)-4-fluoro-benzenesulfonylamide as amorphous solid: Rf(B2) 0.41; ESI-MS: $(M+H)^+$ = 474.

The starting material can be prepared, for example, as follows:

a) Toluene-4-sulfonic acid 2-(2-*tert.*-butoxycarbonylamino-ethoxy)-ethyl ester

To a stirred solution of [2-(2-hydroxy-ethoxy)-ethyl]-carbamic acid tert-butyl ester (CAS No.139115-91-6) (93.7 g) and triethylamine (74.21 ml) in dichloromethane (200 ml) is added a solution of p-toluenesulfonyl chloride (88.82 g) in dichloromethane (250 ml) at 5 °C. The mixture is stirred at 0 °C for 6 h. After addition of *tert.*-butylethylether the triethylamine hydrochloride is removed by filtration. The filtrate is washed with 0.5N aqueous HCl solution, aqueous sodium hydrogen carbonate solution and brine. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give toluene-4-sulfonic acid 2-(2-tert-butoxycarbonylamino-ethoxy)-ethyl ester as a colorless oil: Rf (C3) 0.26.

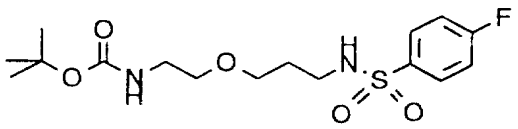
b) [2-(3-Cyano-propoxy)-ethyl]-carbamic acid tert-butyl ester

A suspension of toluene-4-sulfonic acid 2-(2-tert-butoxycarbonylamino-ethoxy)-ethyl ester (61.31 g) and sodium cyanide (25.08 g) in N,N-dimethylformamide (200 ml) is stirred at 50 °C for 4h. N,N-dimethylformamide is removed under reduced pressure. To the residue is added water and the mixture is extracted with tert.-butyl methyl ether. The combined extracts are washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to give [2-(3-cyano-propoxy)-ethyl]-carbamic acid tert-butyl ester as an oil: Rf(C3) 0.19; ESI-MS: $(M+H)^+$=215.

c) [2-(3-Amino-propoxy)-ethyl]-carbamic acid tert-butyl ester

A solution of [2-(3-cyano-propoxy)-ethyl]-carbamic acid tert-butyl ester (11.7 g) in ethanol containing 5% ammonia (200 ml) is stirred in the presence of RaNi (3 g) under hydrogen for 3h. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is purified by flash chromatography to give [2-(3-amino-propoxy)-ethyl]-carbamic acid tert-butyl ester as an oil: Rf (A4) 0.45; ESI-MS: $(M+H)^+$=219.

d) {2-[3-(4-Fluoro-benzenesulfonylamino)-propoxy]-ethyl}-carbamic acid tert-butyl ester



A solution of [2-(3-amino-propoxy)-ethyl]-carbamic acid tert-butyl ester (1.68 g), diiso-propylethylamine (2.63 ml) and p-fluorobenzensulfonyl chloride (1.65 g) in dichloromethane (35 ml) is stirred at 0 °C for 90 min. To the reaction is added water and the mixture is extracted with dichloromethane. The combined extracts are washed with aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue is purified by flash chromatography to give {2-[3-(4-fluoro-benzenesulfonylamino)-propoxy]-ethyl}-carbamic acid tert-butyl ester as an oil: Rf (A1) 0.45; ESI-MS: $(M+H)^+$=377.

e) N-[3-(2-Amino-ethoxy)-propyl]-4-fluoro-benzenesulfonamide trifluoroacetic acid

To a solution of {2-[3-(4-fluoro-benzenesulfonylamino)-propoxy]-ethyl}-carbamic acid tert-butyl ester (2.45 g) in dichloromethane (20 ml) is added trifluoroacetic acid (5 ml) at 0 °C. After stirring at 0 °C for 3h, the solvent is removed under reduced pressure to obtain N-[3-(2-amino-ethoxy)-propyl]-4-fluoro-benzenesulfonamide trifluoroacetic acid as an amorphous solid: Rf(A1) 0.11.

Example 11: 4-(4-Chloro-phenylamino)-2-[3-(N-pyrrolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride

2-Chloro-4-(4-chloro-phenylamino)-8-methoxy-quinazoline hydrochloride (0.64 g) and 3-(N-pyrrolo)-propylamine (prepared as described in *J. Heterocycl. Chem.* **1976**,*13*, 711) (0.33 g) is heated for 0.5 min to produce a melt which is dissolved in isopropanol. The salt of the product is obtained upon addition of a slight excess of 4 N HCl in dioxane. Recrystallization from an isopropanol acetone mixture yields 4-(4-chloro-phenylamino)-2-[3-(N-pyrrolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride, m.p. 247-249 °C.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-8-methoxy-4-(4-chloro-phenylamino)-quinazoline hydrochloride

A solution of 2,4-dichloro-8-methoxy-quinazoline (2.3 g), diisopropyl-ethylamine (5.0 ml) and 4-chloro-aniline (1.5 g) in isopropanol (20 ml) is heated to reflux for 1 h. The cold reaction

mixture is concentrated *in vacuo* and crystallized from diethyl ether to give 2-chloro-8-methoxy-4-(4-chloro-phenylamino)-quinazoline hydrochloride, m.p. 261-262 °C.

b) 2,4-Dichloro-8-methoxy-quinazoline

N,N-Dimethylaniline (0.36 ml) is added slowly to a solution of 8-methoxy-1H,3H-quinazolin-2,4-dione (prepared as described in *J. Chem. Soc.* **1921**, 1425) (1.20 g) in phosphorousoxychloride (3.70 ml) while this mixture is heated up to 125 °C. Refluxing is continued for 10 h after the completion of the addition. Evaporation of the solvent *in vacuo* gives a residue which is added to ice and water. Extraction with ethylacetate yields 2,4-dichloro-8-methoxy-quinazoline, Rf(C4) 0.64.

Example 12: 4-(4-Chloro-phenylamino)-2-[3-(N-imidazolo)-propyl-1-amino]-quinazoline hydrochloride

2-Chloro-4-(4-chloro-phenylamino)-quinazoline hydrochloride (0.765 g) and 3-(N-imidazolo)-propylamine (0.36 ml) is heated for 3 min to produce a melt which is dissolved in isopropanol. The salt of the product is obtained upon addition of a slight excess of 4N HCl in dioxane. Recrystallization from an isopropanol acetone mixture yields 4-(4-chloro-phenylamino)-2-[3-(N-imidazolo)-propyl-1-amino]-quinazoline hydrochloride, Rf(D1) 0.66.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-(4-chloro-phenylamino)-quinazoline

A solution of 2,4-dichloro-quinazoline (19.9 g), diisopropylethylamine (50 ml) and 4-chloro-aniline (14.0 g) in isopropanol (200 ml) is heated to 80 °C for 1 h. The reaction mixture is concentrated *in vacuo*. The residue is chromatographed (silica gel, A2) to yield after crystallization from ethanol ether 2-chloro-4-(4-chloro-phenylamino)-quinazoline: m.p. 170-171 °C, Rf(A1) 0.83

b) 2,4-Dichloro-quinazoline

N,N-Dimethylaniline (114.0 g) is added slowly to a solution of 1H,3H-quinazolin-2,4-dione (146.0 g) in phosphorousoxychloride (535.4 ml) while this mixture is heated up to 140 °C. Refluxing is continued for 20 h after the completion of the addition. The reaction mixture is filtered and evaporated to give a residue which is added to ice and water. The product is

extracted by dichloromethane and crystallized from ether and petrolether to yield 2,4-dichloro-quinazoline, m.p. 115-116 °C.

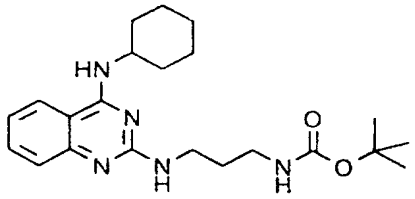
In an analogous manner as described hereinbefore, for example, following compounds can be prepared:

Example 13: N(4)-(4-Chloro-phenylamino)-N(2)-(2-cyclohexylamino-ethyl)-quinazolin-2,4-diamine dihydrochloride
M.p. 295-297 °C.

Example 14: 4-(4-Chloro-phenylamino)-2-[3-(N-pyrrolidino)-propyl-1-amino]-quinazoline hydrochloride
Rf(D1) 0.82.

Example 15: 4-Cyclohexylamino-2-[3-(N-pyrrolo)-propyl-1-amino]-quinazoline hydrochloride
M.p. 132-135 °C

Example 16: [3-(4-Cyclohexylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester



Rf(E1) 0.18.

Example 17: [3-(4-Benzylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester

Benzyl-(2-chloro-quinazolin-4yl)-amine (0.269 g) and (3-amino-propyl)-carbamic acid tert.-butyl ester(0.382 g) is heated for 5 min to produce a melt which is dissolved in methanol and chromatographed (silica gel, C4) to give [3-(4-benzylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester:
Rf(A1) 0.16.

The starting material can be prepared, for example, as follows:

Benzyl-(2-chloro-quinazolin-4yl)-amine

A solution of 2,4-dichloro-quinazoline (3.98 g) and of benzylamine (5.5 ml) in THF (30 ml) is stirred at room temperature for 16 h. The reaction mixture is concentrated *in vacuo*. The residue is crystallization from hot ethanol to yield benzyl-(2-chloro-quinazolin-4yl)-amine: FAB-MS: $(M+H)^+ = 270$.

Example 18: 4-Benzylamino-2-(3-aminopropyl-amino)-quinazolin

[3-(4-Benzylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester (0.130 g) are treated with 4N HCl in dioxane (15 ml) at ambiente temperature for 2 h. Evaporation of the solvent *in vacuo* yields amorphous [3-(4-benzylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester: FAB-MS: $(M+H)^+ = 308$.

Example 19: In a manner analogous to that described hereinbefore, following compounds it can be manufactured:

4-(4-Chloro-phenylamino)-2-[3-(N-pyrrolo)-propyl-1-amino]-quinazoline hydrochloride

4-(4-Chloro-phenylamino)-2-[2-(N-pyrrolo)-ethyl-1-amino]-quinazoline hydrochloride

4-(4-Chloro-phenylamino)-2-[2-(N-imidazolo)-ethyl-1-amino]-quinazoline hydrochloride

4-(4-Chloro-phenylamino)-2-[2-(N-pyrrolidino)-ethyl-1-amino]-quinazoline hydrochloride

4-(4-Chloro-phenylamino)-2-[3-(N-imidazolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride

4-(4-Chloro-phenylamino)-2-[4-(N-imidazolo)-butyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[3-(N-pyrrolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride

4-Cyclohexylamino-2-[3-(N-imidazolo)-propyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[3-(N-pyrrolidino)-propyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[2-(N-pyrrolo)-ethyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[2-(N-imidazolo)-ethyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[2-(N-pyrrolidino)-ethyl-1-amino]-quinazoline hydrochloride

4-Cyclohexylamino-2-[3-(N-imidazolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride

4-Cyclohexylamino-2-[4-(N-imidazolo)-butyl-1-amino]-quinazoline hydrochloride

Example 20: Tablets, each containing 50 mg of active ingredient, for example, naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide hydrochloride, can be prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	500.0 g
Lactose	500.0 g
Potato starch	352.0 g
Gelatin 8.0 g	
Talc 60.0 g	
Magnesium stearate	10.0 g
Silica (highly disperse)	20.0 g
Ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened using an alcoholic solution of the gelatin and granulated by means of a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the highly disperse silica are admixed and the mixture is compressed to give tablets of weight

145.0 mg each and active ingredient content 50.0 mg which, if desired, can be provided with breaking notches for finer adjustment of the dose.

Example 21: Coated tablets, each containing 100 mg of active ingredient, for example, naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide hydrochloride, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.00 g
Lactose	100.00 g
Corn starch	70.00 g
Talc	8.50 g
Calcium stearate	1.50 g
Hydroxypropylmethylcellulose	2.36 g
Shellac	0.64 g
Water	q.s.
Dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened and granulated with a paste prepared from 15 g of corn starch and water (with warming). The granules are dried, and the remainder of the corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to give tablets (weight: 280 mg) and these are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the coated tablet: 283 mg).

Example 22: Tablets and coated tablets containing another compound of the formula I or a pharmaceutically acceptable salt of a compound of the formula I, for example as in one of Examples 1 to 19, can also be prepared in an analogous manner to that described in Examples 20 and 21

SEQUENCE LISTING

(1) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1501 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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 65                  70                  75                  80

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                 85                  90                  95

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Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met
        115                 120                 125

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Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
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AAT TTA ACG GCA AAC CAT GGC TAC TTC CTG ATA GCT ACT GTC TGG ACA        588
Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
                165                 170                 175

CTG GGC TTT GCC ATC TGT TCT CCC CTC CCA GTG TTT CAC AGT CTT GTG        636
Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
            180                 185                 190

GAA CTT AAG GAG ACC TTT GGC TCA GCA CTG CTG AGT AGC AAA TAT CTC        684
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TCT TTA TTG CTA GTG CAG TAT ATC CTG CCT CTA GTA TGT TTA ACG GTA        780
Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
225                 230                 235                 240

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Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys
                245                 250                 255

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            260                 265                 270

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305                 310                 315                 320

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                325                 330                 335

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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                20                  25                  30

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Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
65                  70                  75                  80

Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
                85                  90                  95

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            100                 105                 110

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385                 390                 395                 400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
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Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
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(3) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1457 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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GTTTCCCTCT GAATAGATTA ATTTAAAGTA GTCATGTAAT GTTTTTTTGG TTGCTGACAA      60

ATG TCT TTT TAT TCC AAG CAG GAC TAT AAT ATG GAT TTA GAG CTC GAC      108
Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp
  1               5                  10                  15

GAG TAT TAT AAC AAG ACA CTT GCC ACA GAG AAT AAT ACT GCT GCC ACT      156
Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr
             20                  25                  30

CGG AAT TCT GAT TTC CCA GTC TGG GAT GAC TAT AAA AGC AGT GTA GAT      204
Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp
         35                  40                  45

GAC TTA CAG TAT TTT CTG ATT GGG CTC TAT ACA TTT GTA AGT CTT CTT      252
Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu
     50                  55                  60
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GGC TTT ATG GGG AAT CTA CTT ATT TTA ATG GCT CTC ATG AAA AAG CGT        300
Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg
 65                  70                  75                  80

AAT CAG AAG ACT ACG GTA AAC TTC CTC ATA GGC AAT CTG GCC TTT TCT        348
Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser
                 85                  90                  95

GAT ATC TTG GTT GTG CTG TTT TGC TCA CCT TTC ACA CTG ACG TCT GTC        396
Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val
            100                 105                 110

TTG CTG GAT CAG TGG ATG TTT GGC AAA GTC ATG TGC CAT ATT ATG CCT        444
Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro
        115                 120                 125

TTT CTT CAA TGT GTG TCA GTT TTG GTT TCA ACT TTA ATT TTA ATA TCA        492
Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser
    130                 135                 140

ATT GCC ATT GTC AGG TAT CAT ATG ATA AAA CAT CCC ATA TCT AAT AAT        540
Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn
145                 150                 155                 160

TTA ACA GCA AAC CAT GGC TAC TTT CTG ATA GCT ACT GTC TGG ACA CTA        588
Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu
                165                 170                 175

GGT TTT GCC ATC TGT TCT CCC CTT CCA GTG TTT CAC AGT CTT GTG GAA        636
Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu
            180                 185                 190

CTT CAA GAA ACA TTT GGT TCA GCA TTG CTG AGC AGC AGG TAT TTA TGT        684
Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys
        195                 200                 205

GTT GAG TCA TGG CCA TCT GAT TCA TAC AGA ATT GCC TTT ACT ATC TCT        732
Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser
    210                 215                 220

TTA TTG CTA GTT CAG TAT ATT CTG CCC TTA GTT TGT CTT ACT GTA AGT        780
Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser
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225                 230                 235                 240

CAT ACA AGT GTC TGC AGA AGT ATA AGC TGT GGA TTG TCC AAC AAA GAA      828
His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu
                245                 250                 255

AAC AGA CTT GAA GAA AAT GAG ATG ATC AAC TTA ACT CTT CAT CCA TCC      876
Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser
            260                 265                 270

AAA AAG AGT GGG CCT CAG GTG AAA CTC TCT GGC AGC CAT AAA TGG AGT      924
Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser
        275                 280                 285

TAT TCA TTC ATC AAA AAA CAC AGA AGA AGA TAT AGC AAG AAG ACA GCA      972
Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala
    290                 295                 300

TGT GTG TTA CCT GCT CCA GAA AGA CCT TCT CAA GAG AAC CAC TCC AGA     1020
Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg
305                 310                 315                 320

ATA CTT CCA GAA AAC TTT GGC TCT GTA AGA AGT CAG CTC TCT TCA TCC     1068
Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser
                325                 330                 335

AGT AAG TTC ATA CCA GGG GTC CCC ACT TGC TTT GAG ATA AAA CCT GAA     1116
Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu
            340                 345                 350

GAA AAT TCA GAT GTT CAT GAA TTG AGA GTA AAA CGT TCT GTT ACA AGA     1164
Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg
        355                 360                 365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA     1212
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
    370                 375                 380

TTA GTA TTT GCT GTT AGT TGG ATG CCA CTA CAC CTT TTC CAT GTG GTA     1260
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val
385                 390                 395                 400

ACT GAT TTT AAT GAC AAT CTT ATT TCA AAT AGG CAT TTC AAG TTG GTG     1308
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Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

TAT TGC ATT TGT CAT TTG TTG GGC ATG ATG TCC TGT TGT CTT AAT CCA      1356
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

ATT CTA TAT GGG TTT CTT AAT AAT GGG ATT AAA GCT GAT TTA GTG TCC      1404
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser
        435                 440                 445

CTT ATA CAC TGT CTT CAT ATG TAA TAA TTCTCACTGT TTACCAAGGA        1452
Leu Ile His Cys Leu His Met  *   *
    450                 455

AAGAAC                                                          1457
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(41) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp
  1               5                  10                  15

Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr
            20                  25                  30

Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp
        35                  40                  45

Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu
    50                  55                  60
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Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg
 65                  70                  75                  80

Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser
                 85                  90                  95

Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val
            100                 105                 110

Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro
        115                 120                 125

Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser
    130                 135                 140

Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn
145                 150                 155                 160

Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu
                165                 170                 175

Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu
            180                 185                 190

Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys
        195                 200                 205

Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser
    210                 215                 220

Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser
225                 230                 235                 240

His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu
                245                 250                 255

Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser
            260                 265                 270

Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser
        275                 280                 285

Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala
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    290                 295                 300

Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg
305                 310                 315                 320

Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser
                325                 330                 335

Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu
            340                 345                 350

Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg
        355                 360                 365

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
    370                 375                 380

Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val
385                 390                 395                 400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser
        435                 440                 445

Leu Ile His Cys Leu His Met  *    *
    450
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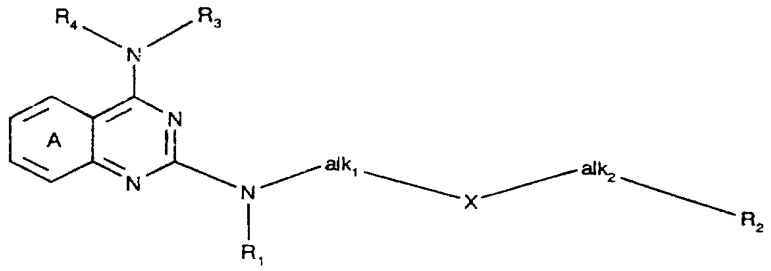
What is claimed is

1. Use of a compound of formula (I)



in which

alk_1 and alk_2, independently of one another, represent, independently of one another, a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined

below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being $-CH_2-$, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or--$C(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or

heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;or or a pharmaceutically accetable salt thereof for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype.

2. Use according to claim 1 for the manufacture of a pharmaceutical composition for the prophylaxis and the treatment of disorders or disease states caused by eating disorders, of

obesity, bulimia nervosa, diabetes, dyspilipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

3. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, $-NR_1$-CO-O-R, $-NR_1$-CO-R, $-NR_1$-CO-NR_1-R, $-NR_1$-SO_2-R, $-NR_1$-SO_2-NR_1-R, $-SO_2$-R, $-SO_2$-NR_1-R, or $-SO_2$-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group $-N(R)(R_1)$ represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_1(X_2)(X_3)$ wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula $-X_4$-$(CO)_p$-$(CH_2)_o$-, $-(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or $-(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being $-CH_2$-, $-N(R_1)$- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2$-;];

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

4. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy or lower alkoxy-lower alkoxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

R_3 represents

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and N-substituted carbamoyl;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, or -CO-;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) substituted amino;

(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl, pyrrolyl, imidazolyl, or pyridyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

5. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, phenyl, or phenyl-lower alkyl;

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl;

(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents hydrogen, lower alkyl, lower alkyl which substituted by lower alkoxy or di-lower alkylamino, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond, 1,2-ethenylene, or -CO-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

6. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represents a single bond; or C_1-C_4-alkylene;

R_1 represents hydrogen;

R_2 represents (i) hydrogen, halogen, cyano, lower alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-lower alkyl, phenyl, phenyl-lower alkyl, or pyrrolyl, imidazolyl;
(ii) amino, amino which is mono-substituted by C_3-C_6-cycloalkyl, amino which is disubstituted by lower alkyl or by C_4-C_6-alkylene or amino which is mono-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;
(iii) a group selected from -NR_1-SO_2-R, R being lower phenyl or naphthyl;

R_3 represents hydrogen, C_3-C_6-cycloalkyl-lower alkyl, phenyl-lower alkyl, lower alkyl which substituted by di-lower alkylamino, C_3-C_6-cycloalkyl, or phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents a single bond or -O-;

wherein any aryl moiety, if not designated otherwise and the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy .

7. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents (i) phenyl which is substituted by halogen, especially 4-halo-phenyl, or pyrrolyl, especially 1-pyrrolyl or (ii) -NH-SO_2-R and R being naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

8. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 represent C_2-C_4-alkylene;

R_2 represents (i) phenyl which is substituted by halogen, especially 4-halo-phenyl, or pyrrolyl, especially 1-pyrrolyl or (ii) -NH-SO_2-R and R being naphthyl; and, in each case,

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen; and

X represents a single bond;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

9. A compound of formula (I) or a salt thereof in which;

alk_1 and alk_2, independently of one another, represent, independently of one another, a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(v) carbamoyl or N-substituted carbamoyl;
(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or
(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents a single bond, 1,2-ethenylene, 1,2-ethynylene, -O-, -S(O)n-, -CO- or-$(OR')_2$-; one of R' being hydrogen or both being each lower alkyl or being together lower alkylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy,

oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

10. A compound according to claim 9 of formula (I) or a salt thereof selected from the group consisting of
naphthalene-1-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide;
naphthalene-1-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide;
naphthalene-1-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide;
naphthalene-2-sulfonic acid [6-(4-amino-quinazolin-2-ylamino)-hexyl]-amide;
naphthalene-2-sulfonic acid [8-(4-amino-quinazolin-2-ylamino)-octyl]-amide;
naphthalene-2-sulfonic acid [7-(4-amino-quinazolin-2-ylamino)-heptyl]-amide;
naphthalene-1-sulfonic acid {6-[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-hexyl}-amide hydrochloride;
n-(3-{2-[4-(cyclopropylmethyl-amino)-quinazolin-2-ylamino]-ethoxy}-propyl)-4-fluoro-benzenesulfonylamide;
4-(4-chloro-phenylamino)-2-[3-(N-pyrrolo)-propyl-1-amino]-8-methoxy-quinazoline hydrochloride;
4-(4-chloro-phenylamino)-2-[3-(N-imidazolo)-propyl-1-amino]-quinazoline hydrochloride;
N(4)-(4-chloro-phenylamino)-N(2)-(2-cyclohexylamino-ethyl)-quinazolin-2,4-diamine dihydrochloride;
4-(4-chloro-phenylamino)-2-[3-(N-pyrrolidino)-propyl-1-amino]-quinazoline hydrochloride;
4-cyclohexylamino-2-[3-(N-pyrrolo)-propyl-1-amino]-quinazoline hydrochloride;
[3-(4-cyclohexylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester;
[3-(4-benzylamino-quinazolin-2-yl-amino)-propyl]-carbamic acid tert.-butyl ester; and
4-benzylamino-2-(3-aminopropyl-amino)-quinazolin.

11. A pharmaceutical composition for the treatment of diseases or disorders associated with NPY Y5 receptor subtype comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 and a carrier.

12. A method for the treatment and prophylaxis of disorders or disease states associated with NPY Y5 receptor subtype comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/EP 96/05056

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/95 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 2, 1981, WASHINGTON US, pages 127-140, XP002029206 E. ELSLAGER ET AL.: "SYNTHESIS AND ANTIMALARIAL EFFECTS OF N2-ARYL-N4-(DIALKYLAMINOALKYL) AND N4-ARYL-N2-(DIALKYLAMINOALKYL)-2,4-QUINAZOLINDIAMINES." see page 127 - page 139 ---	1,9
X	FR 926 577 A (I.C.I.) 6 October 1947 see page 1 - page 8 ---	1,9
X	US 3 956 495 A (W.LACEFIELD) 11 May 1976 see column 1 - column 19 ---	1,9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1997	17. 04. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Francois, J

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/05056

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 389 613 A (SYNTHELABO) 1 December 1978 see claims; tables 1,6	1,9
A	EP 0 225 866 A (GEROT-PHARMAZEUTIKA) 16 June 1987 see page 1 - page 8	1,9

1

INTERNATIONAL SEARCH REPORT

International application No.
I/EP 96/05056

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of the human body, the search has been carried out and based on the attributed effects of the compounds. (Rule 39.1(IV))

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Claims searched completely: 5-8, 10-12
Claims searched incompletely: 1-4, 9
see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 96/ 05056

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The considerable longlist of substituents with their numerous and cascading significances makes that the present application hardly meets the requirements of Art. 6; a complete search is not possible on economic grounds and has been limited to the examples and related compounds. (Guidelines Chap. B III 3.6)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ıal Application No
PCT/EP 96/05056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 926577 A		NONE	
US 3956495 A	11-05-76	US 4048312 A	13-09-77
FR 2389613 A	01-12-78	NONE	
EP 225866 A	16-06-87	AT 384218 A	12-10-87
		DE 3681701 A	31-10-91
		JP 62132869 A	16-06-87
		US 4795750 A	03-01-89